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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,152	03/20/2002	Heinrich Leonhardt	101195-70	6299

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	6

DATE MAILED: 09/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,152	LEONHARDT ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment filed 20 March 2002 (Paper No. 4) has been received and entered in full. Claims 6-9 have been cancelled. Claims 1-5 are under examination.

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims **1-5** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated fusion protein selected from the group consisting of VP22-SV40 T antigen, VP22-viral cyclin K, and VP22-viral cyclin V*, does not reasonably provide enablement for *a tissue regenerating agent or other fusion proteins*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

4. The claims are drawn very broadly to a tissue regenerating agent comprising a fusion protein derived from a peptide sequence which effects uptake in cells and comprising a protein inducing the proliferation of cells. The language of said claims encompasses two large geneses of proteins, those which effect uptake in cells and proliferation inducing proteins as well as *in vitro* and *in vivo* use of the "tissue regeneration agent".

5. The specification teaches a fusion protein comprising VP22 and SV40 T-antigen with a His tag, and VP22 fused to cyclin K or cyclin V.

6. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed product as a tissue regenerating agent in a patient. The specification fails to provide any guidance for the successful use of the VP22-SV40 T-antigen fusion protein or other fusion proteins which are species of the genus of an uptake protein fused to a proliferation inducing protein, and since resolution of the various complications in regards to targeting the role an agent in tissue regeneration is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations unspecified fusion proteins, administration protocols, dosages, and then signs and symptoms of tissue regeneration to correlate with said fusion protein.

7. In essence, it is an invitation to experiment for the skilled artisan. The skilled artisan first must determine which proteins which effect uptake in cells and other that induce proliferation in cells are appropriate for use. Then clone and construct the fusion proteins. Following this, the

skilled artisan must administer said test fusion proteins to animal models or patients to determine which if any have the desired effect. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

8. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide expression level *in vivo* based solely on the postulated performance of a single untested fusion protein is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed fusion proteins in *in vivo* therapeutic methods, such a disclosure would not be considered enabling since the state of tissue regeneration, especially for cardiac and nervous system tissue, is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

9. The following references are cited herein to illustrate the state of the art of VP22 fusion proteins.

10. On the breadth of the claims, Elliott and O'Hare (1999) "Intracellular Trafficking of VP22-GFP fusion proteins." Gene Therapy **6**: 149-151 teach that VP22 fusion proteins may be expressed at levels to low to allow the full activity of the fusion protein. In this case, the VP22-GFP protein was expressed at levels too low to detect in live cells (Figure 2). The authors note that: "It is difficult to predict how much of a component is required to elicit a biological effect, but clearly many regulatory proteins or enzymes function at relatively low physiological concentrations." (pp. 151) Thus due to the breath of the claims, the skilled artisan is confronted with a level of unpredictability whether or not a given fusion protein partner of VP22 will be expressed at sufficient levels, correctly fold, or have a sufficient half-life such that it is biologically active.

11. On the nature of the invention, Derer *et al.* (1999) "Direct protein transfer to terminally differentiated muscle cells." J. Mol. Med. 77: 609-613 teach that a VP22-GFP fusion protein can successfully enter terminally differentiated cells, in this case myotubes (Figure 3). However, the authors note that in the unfused myotubes in the same experiment showed only nuclear localization of the VP22-GFP fusion protein versus predominately cytoplasmic localization (pp. 613). Thus a VP22 fusion protein may not accumulate in the correct subcellular compartment (cytosol versus nucleoplasm) as to be useful as a "tissue regeneration agent" for a terminally differentiated cell even though it may enter said cell. Also, as noted above, even if the protein makes it to the correct or desired subcellular location, it may not be active or present in a sufficient amount as to be biologically active. Thus the skilled artisan is confronted with an undue experimentation burden of trail and error to determine which fusion protein combinations work.

12. On working examples, Derer *et al.* (16 January 2002) "A novel approach to induce cell cycle reentry in terminally differentiated muscle cells." FASEB J. **16**(1): 132-133 teach a post-filing reduction to practice of a VP22-SV40 fusion protein which is capable of entering terminally differentiated muscle cells (Figure 1). However, this reference does not provide support for "tissue regeneration" but in fact shows that the VP22-SV40 protein, *in vitro*, can stimulate mitosis but not act as a "tissue regeneration agent". It is noted that "tissue regeneration" can be understood to mean the revival of dead cells which is not show by said reference.

13. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from prophetic considerations of the possible effects of a single member of a large genus to the *in vivo* therapeutic use as a tissue regeneration agent as exemplified in the references herein.

14. Claims **1-3** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. The phrase "a protein or peptide sequence which effects uptake in cells" in claims 1 and 3 is a relative term which renders the claim indefinite. The phrase "a protein or peptide sequence which effects uptake in cells" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of said phrase are not clear from the prior art or the Specification.

16. The phrase "a protein inducing the proliferation of cells" in claim 1 is a relative term which renders the claim indefinite. The phrase " a protein inducing the proliferation of cells" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of said phrase are not clear from the prior art or the Specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

17. Claims **1 and 2** are rejected under 35 U.S.C. 102(e) as being anticipated by US 6017735 (25 January 2000) O'Hare & Elliott. US 6017735 teaches a fusion protein comprising VP22 fused to a protein for cell cycle control (claim 1). This includes growth factors such as GM-CSF, M-CSF, G-CSF which may be construe as "a protein for inducing the proliferation of cells" thus meeting the limitations of claims 1 and 2 (Col. 12 lines 34-50).

18. Claims **1, 2, 3, and 4** are rejected under 35 U.S.C. 102(e) as being anticipated by US 6358739 (19 March 2002) Baetge *et al.* US 6358739 teaches a fusion protein comprising VP22 fused to SV40 large T antigen or SV40 small T antigen thus meeting the limitations of claims 1-4 (claims 1 and 2).

Summary

19. Claims 1-5 are hereby rejected.

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

a. US 6184038 B1 (6 February 2001) O'Hare & Elliott

b. US 6251398 B1 (26 June 2001) O'Hare & Elliott

c. US 6451601 (17 September 2002) Baetge

d. US 6521455 B2 (18 February 2003) O'Hare & Elliott

e. US Patent Application Publication US 2003/0119770 A1 (26 June 2003) Lai *et al.*

f. Brewis *et al.* (January 2000) "Evaluation of VP22 Spread in Tissue Culture." Journal of Virology **74**(2): 1051-1056

g. Zender *et al.* (2002) "VP22-mediated intercellular transport of p53 in hepatoma cells *in vitro* and *in vivo*." Cancer Gene Therapy **9**: 489-496

h. Wills *et al.* (September 2001) " Intratumoral Spread and Increased Efficacy of a p53-VP22 Fusion Protein Expressed by a Recombinant Adenovirus." Journal of Virology **75**(18): 9733-9741

i. Soden *et al.* (2002) "Genetic engineering of the glucocorticoid receptor by fusion with the herpes viral protein VP22 causes selective loss of transctivation." Journal of Endocrinology **172**: 615-625

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
September 3, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER